Reduced-Intensity Delayed Intensification in Standard-Risk Pediatric Acute Lymphoblastic Leukemia Defined by Undetectable Minimal Residual Disease: Results of an International Randomized Trial (AIEOP-BFM ALL 2000)

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Abstract: Purpose Delayed intensification (DI) is an integral part of treatment of childhood acute lymphoblastic leukemia (ALL), but it is associated with relevant toxicity. Therefore, standard-risk patients of trial AIEOP-BFM ALL 2000 (Combination Chemotherapy Based on Risk of Relapse in Treating Young Patients With ALL) were investigated with the specific aim to reduce treatment intensity. Patients and Methods Between July 2000 and July 2006, 1,164 patients (1 to 17 years of age) with standard-risk ALL (defined as the absence of high-risk cytogenetics and undetectable minimal residual disease on days 33 and 78) were randomly assigned to either experimental reduced-intensity DI (protocol III; P-III) or standard DI (protocol II; P-II). Cumulative drug doses of P-III were reduced by 30% for dexamethasone and 50% for vincristine, doxorubicin, and cyclophosphamide, which shortened the treatment duration from 49 to 29 days. The study aimed at noninferiority of reduced-intensity P-III; analyses were performed according to treatment given. Results For P-III and P-II, respectively, the 8-year rate of disease-free survival (± SE) was 89.2 ± 1.3% and 92.3 ± 1.2% (P = .04); cumulative incidence of relapse, 8.7 ± 1.2% and 6.4 ± 1.1% (P = .09); and overall survival, 96.1 ± 0.8% and 98.0 ± 0.6% (P = .06). Patients with ETV6-RUNX1-positive ALL and patients 1 to 6 years of age performed equally well in both arms. The incidence of death during remission was comparable, which indicates equivalent toxicity. The 8-year cumulative incidence rate of secondary malignancies was 1.3 ± 0.5% and 0.6 ± 0.4% for P-III and P-II, respectively (P = .37). Conclusion Although the criteria used for the standard-risk definition in this trial identified patients with exceptionally good prognosis, reduction of chemotherapy was not successful mainly because of an increased rate of relapse. The data suggest that treatment reduction is feasible in specific subgroups, which underlines the biologic heterogeneity of this cohort selected according to treatment response.

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Between July 2000 and July 2006, 1,164 patients (1 to 17 years of age) with standard-risk ALL (defined as the absence of high-risk cytogenetics and undetectable minimal residual disease on days 33 and 78) were randomly assigned to either experimental reduced-intensity DI (protocol III; P-III) or standard DI (protocol II; P-II). Cumulative drug doses of P-III were reduced by 30% for dexamethasone and 50% for vincristine, doxorubicin, and cyclophosphamide, which shortened the treatment duration from 49 to 29 days. The study aimed at noninferiority of reduced-intensity P-III; analyses were performed according to treatment given.

Results
For P-III and P-II, respectively, the 8-year rate of disease-free survival (± SE) was 89.2 ± 1.3% and 92.3 ± 1.2% (P = .04); cumulative incidence of relapse, 8.7 ± 1.2% and 6.4 ± 1.1% (P = .09); and overall survival, 96.1 ± 0.8% and 98.0 ± 0.6% (P = .06). Patients with ETV6-RUNX1-positive ALL and patients 1 to 6 years of age performed equally well in both arms. The incidence of death during remission was comparable, which indicates equivalent toxicity. The 8-year cumulative incidence rate of secondary malignancies was 1.3 ± 0.5% and 0.6 ± 0.4% for P-III and P-II, respectively (P = .37).

Conclusion
Although the criteria used for the standard-risk definition in this trial identified patients with exceptionally good prognosis, reduction of chemotherapy was not successful mainly because of an increased rate of relapse. The data suggest that treatment reduction is feasible in specific subgroups, which underlines the biologic heterogeneity of this cohort selected according to treatment response.

Introduction
Over the past decades, the prognosis for children and adolescents with acute lymphoblastic leukemia (ALL) has improved considerably. Advances were mainly accomplished through refinement of biologic characterization, risk group assignment, and risk-stratified treatment. The assessment of minimal residual disease (MRD) has introduced unsurpassed precision in the differentiation between patients with a high risk of relapse and those with a low risk. Prospectively developed in the 1990s, MRD measured by immunoglobulin/ T-cell receptor gene rearrangement polymerase chain reaction (PCR-MRD) was implemented for risk stratification in the trial, Combination Chemotherapy Based on Risk of Relapse in Treating Young Patients with Acute Lymphoblastic Leukemia (AIEOP-BFM ALL 2000).
With increasing survival rates, therapy-related morbidity and mortality as well as long-term sequelae have increasingly moved into focus.\(^8,9\) Especially for patient groups with the most favorable prognosis, several leukemia study groups have strived for a reduction of treatment burden without jeopardizing outcome.\(^10-14\) In former trials, the ALL–Berlin-Frankfurt-Münster (BFM) study group demonstrated the importance of delayed intensification in the treatment of patients with low-risk ALL. The reintensification element protocol II (P-II) significantly improved the outcome of high-risk patients in ALL-BFM 76.\(^15\) The reintensification element (protocol III [P-III]) also was implemented for low-risk patients in ALL-BFM 79.\(^16,17\) ALL-BFM 83 focused again on reduction of treatment burden in low-risk patients by testing treatment with and without P-III, which yielded results in favor of reinduction (10-year probable event-free survival [pEFS] rate, 81 ± 5% v 56 ± 6%).\(^16,18\)

In the era of improved risk assignment, the question of the adequate chemotherapeutic intensity needed to ensure consistently low relapse rates was again addressed in a cooperative prospective trial jointly conducted by two large leukemia study groups—Associazione Italiana di Ematologia e Oncologia Pediatrica (AIEOP) and Berlin-Frankfurt-Münster (BFM)—in AIEOP-BFM ALL 2000. The randomized trial compared standard delayed intensification (P-II) with a reduced-intensity regimen (P-III) in a cohort of standard-risk (SR) patients with favorable treatment response defined by PCR-MRD. Herein, we report the results of this trial.

**Study Design**

Patients 1 to 17 years of age with ALL in one of the participating centers in Italy, Germany, Austria, and Switzerland were registered in the
AIEOP-BFM ALL 2000 trial after written informed consent from their guardians. Routine initial diagnostics were cytology, immunophenotyping, and molecular genetic screening for the presence of ETV6-RUNX1, BCR-ABL1, and KMT2A-AFF1 (MLL-AF4) fusion transcripts. Response assessment was performed by early cytologic assessment as well as by PCR-MRD on the basis of immunoglobulin and T-cell receptor gene rearrangements. The respective standard procedures have been published previously.\(^2,3,7,18-21\)

Good response or poor response to a 7-day prednisone prephase plus one intrathecal dose of methotrexate were defined as \(< \text{1.0 } \times 10^9/L\) and \(\geq \text{1.0 } \times 10^9/L\) blasts in peripheral blood, respectively. Complete remission (CR) was defined as \(< 5\%\) blasts in regenerating bone marrow at the end of induction treatment and the absence of extramedullary disease. Relapse was defined as either recurrence of \(\geq 25\%\) lymphoblasts in bone marrow or localized leukemic infiltrate at any site after having achieved CR.

Risk group assignment to the high-risk group in AIEOP-BFM ALL 2000 was based on genetic characterization of ALL (presence of BCR-ABL1, KMT2A-AFF1) and slow cytologic and molecular response to treatment (prednisone poor response, no CR on day 33, or MRD \(\geq 5 \times 10^{-4}\) on day 78). In the absence of the aforementioned high-risk criteria, patients were assigned to the SR group if MRD was negative on days 33 and 78 with at least two markers with a sensitivity of \(1 \times 10^{-4}\). The remainder of the patients without high-risk criteria was assigned to the medium-risk group.

The study protocol was approved by the competent ethics committees of the national coordinating centers (San Gerardo Hospital, Monza, Italy; Hannover Medical School, Hannover, Germany; St Anna Children’s Hospital, Vienna, Austria; and University Children’s Hospital, Zürich, Switzerland) and registered as clinical trials (ClinicalTrials.gov identifiers: NCT00430118 [BFM] and NCT00613457 [AIEOP]). A data safety and monitoring committee periodically supervised the study progress.

**Randomization and Treatment**

Only SR patients were eligible for random assignment. They were assigned to receive either the experimental, less-intensive P-III or the standard P-II as delayed intensification. Random assignment was performed

**Fig 3.** (A) Disease-free survival (DFS), (B) cumulative incidence of relapse (CIR), and (C) overall survival (OS) in the as-treated analysis. HR, hazard ratio; pDFS, probability of DFS; P-II, protocol II; P-III, protocol III.
### Table A

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**Hazard Ratio and 95% CI**

### Table B

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<td>PDN</td>
<td>584 (50.2)</td>
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**Hazard Ratio and 95% CI**

### Figure 4

Forest plot of hazard ratio by patient subgroup for (A) disease-free survival (DFS), (B) cumulative incidence of relapse (CIR), and (C) overall survival (OS). (*) Data refer to patients with successful investigation of the respective criteria. DXM, dexamethasone in induction treatment; pDFS, probability of DFS; PDN, prednisone in induction treatment; P-II, protocol II; P-III, protocol III; pOS, probability of OS.
centrally by each country’s data center in accordance with random permuted blocks. This randomization was stratified by allocation to a preceding random assignment (dexamethasone vs prednisone) and treatment center.22

P-III was shorter than P-II (duration, 28 v 49 days), and its cumulative drug doses were reduced by 30% for dexamethasone and 50% for vincristine, doxorubicin, and cyclophosphamide compared with P-II. An outline of the SR treatment of AIEOP-BFM ALL 2000 is shown in Figure 1, with drug doses also listed in the Data Supplement. P-II and P-III are split into two parts. The first part lasts from day 1 to 29 in P-II and from day 1 to 14 in P-III, whereas the second part lasts from days 36 to 49 in P-II and from days 15 to 28 in P-III. Details on stratification, prognostic impact of MRD, and results of the random assignments during induction (dexamethasone 10 mg/m²/day vs prednisone 60 mg/m²/day) have been published previously.23,24 Criteria for cranial irradiation are listed in the Data Supplement.

**Statistical Analysis**

The primary outcome was disease-free survival (DFS) because all patients were in CR at random assignment. DFS was defined as the time from random assignment to the date of last follow-up or first event. Events were relapse, secondary neoplasm, or death from any cause. Secondary end points were overall survival (OS) defined as time to death from any cause, or last follow-up, and treatment-associated toxicities.

The objective of this randomized trial was to prove noninferiority of the reduced-intensity treatment compared with standard treatment. The main analysis was planned as a per-protocol evaluation of 4-year DFS. All randomly assigned patients were included in this analysis, but patients who switched trial arms were included in the treatment arm actually given. In addition, an intent-to-treat analysis was performed. The Kaplan-Meier method was used to estimate survival probabilities; differences between groups were compared by log-rank test.25 Cumulative incidence functions for competing events were constructed by the method of Kalbfleisch and Prentice and were compared with Gray’s test.24,25 The Cox proportional hazard regression model was used for univariable and multivariable analyses.24 A sample size of 1,024 randomly assigned patients was considered appropriate to assess noninferiority (Δ < 4%) with 90% power under the assumption of a 96% 4-year DFS in the reference arm. Two interim analyses were planned 3 and 4 years after start of inclusion. For safety reasons, the interim analysis was a log-rank test of difference instead of the equivalence test planned for the final analysis.

**RESULTS**

**Patient Characteristics**

From July 1, 2000, to June 30 (July 31 for AIEOP), 2006, 4,937 patients were enrolled in AIEOP-BFM ALL 2000, of whom 98 were not eligible for evaluation (Fig 2). Among 1,346 SR patients eligible for random assignment, 182 were not assigned. The remaining 1,164 patients entered the randomized comparison; 581 children were allocated to the experimental arm P-III and 583 to the standard arm P-II. We observed no significant differences in initial patient characteristics among randomly assigned versus nonrandomly assigned patients as well as between the two arms analyzed by intention to treat or treatment given (Data Supplemental).

**Treatment Outcome**

After a median follow-up of 8.6 years, analysis per treatment given revealed a 4-year probability of DFS (pDFS ± SE) rate of
91.8 ± 1.1% in the reduced-intensity P-III arm (n = 584) and of 95.8 ± 0.8% in the P-II arm (n = 579; P = .04) on the basis of the occurrence of 62 versus 42 events, respectively (Fig 3). The lower limit of the one-sided 95% CI for the pDFS rates was −6.4%, which is far below the noninferiority margin of −4% (P = .005 for difference of the 4-year pDFS estimates). The respective results at 8 years were 89.2 ± 1.3% and 93.2 ± 1.2% for pDFS (P = .041 and 8.7 ± 1.2% and 6.4 ± 1.1% for cumulative incidence of relapse (CIR; P-III v P-II, P = .09; Fig 3). The 8-year OS rate was 96.1 ± 0.8% and 98.0 ± 0.6% (P = .06). The intent-to-treat analysis gave almost identical results (Data Supplement).

These differences of treatment outcome held for virtually all clinical and biologic subgroups, although in many subgroups the differences did not reach statistical significance (Figs 4A to 4C). ETV6-RUNX1 status and age at diagnosis represented the only exception. Eight-year pDFS rates of patients with ETV6-RUNX1−negative ALL were 86.2 ± 1.9% versus 91.1 ± 1.6% (P = .037) and for patients with ETV6-RUNX1−positive ALL, 94.5 ± 1.7% versus 94.4 ± 1.8% (P = .74) for P-III versus P-II, respectively (Figs 5A and 5B). Analogous results held for age at diagnosis. For patients 1 to 10 years of age, the 8-year pDFS rate was 90.7 ± 1.4% versus 92.4 ± 1.2% (P = .26), and for patients age ≥ 10 years, 81.6 ± 4.0% versus 90.3 ± 4.1% (P = .04) for P-III versus P-II, respectively (Figs 5C and 5D).

The patterns of relapse with respect to time after diagnosis were different after P-III and P-II. The proportion of early relapses (ie, within 2.5 years after diagnosis) was higher in P-III than in P-II (P-III, 19 [38.0%] of 50 relapses; P-II, 10 [28.6%] of 35 relapses); the same occurred for late relapses (2.5 to < 5 years after diagnosis; P-III, 23 [46.0%] of 50 relapses; P-II, 10 [28.6%] of 35 relapses), but a significantly higher proportion for very-late relapse (≥ 5 years after diagnosis) was observed in patients treated...
Secondary malignancies occurred in seven patients who received P-III (myelodysplastic syndrome (n = 2); CNS tumor (n = 2); acute myeloid leukemia (n = 2); and non-Hodgkin lymphoma (n = 1) and in four patients who received P-II (myelodysplastic syndrome (n = 2); acute myeloid leukemia (n = 1); and solid tumor (n = 1). This finding corresponds to an 8-year cumulative incidence rate of secondary malignancy of 1.3 ± 0.5% and 0.6 ± 0.4% for patients given P-III and P-II, respectively ($P = .37$; Table 1).

An interaction between the initial corticosteroid in induction and outcome after random assignment has not been observed (Fig 4). Outcome by National Cancer Institute (NCI) criteria was an 8-year pDFS rate of 91.6 ± 1.4% versus 92.8 ± 1.3% ($P = .36$), a CIR rate of 7.0 ± 1.2% versus 6.2 ± 1.2% ($P = .49$), and an 8-year OS rate of 97.9 ± 0.7% versus 98.1 ± 0.7% ($P = .77$) for NCI SR for P-III and P-II, respectively. For NCI high risk, the 8-year pDFS rate was 82.9 ± 3.1% versus 90.4 ± 2.7% ($P = .041$); CIR rate, 13.0 ± 2.8% versus 7.5 ± 2.5% ($P = .07$); and 8-year OS rate, 91.3 ± 2.3% versus 97.7 ± 1.3% ($P = .021$) for P-III and P-II, respectively.

Toxicity

The incidence of death during remission was comparable, with 0.9 ± 0.4% (n = 5) and 0.7 ± 0.3% (n = 4) for P-III and P-II, respectively. The same applies for the number of adverse events, which was essentially the same in the two arms (Table 2). Life-threatening events, however, were slightly more likely to happen with P-II (n = 10) than with P-III (n = 7).

If analyzed separately for the first and the second phases of P-II and P-III, life-threatening adverse events were mostly observed in the first phase of P-II, whereas patients treated with P-III suffered from adverse events more frequently in the second phase of P-III. The median time needed until start of the second part of P-III or P-II was 15 days (n = 184 with data available) and 44 days...
showed a signifi-
cantly inferior to those obtained with the standard treatment. DFS data
demonstrated that patients in P-III by the treating physicians, which is probably
attributable to an underestimation of the impact of this treatment
element. This hypothesis is supported by the significantly shorter
treatment delay between both parts of the respective treatment phase (2 days in P-III v 14 days in P-II). Patients treated with P-III thus
experienced a higher dose density than patients treated with P-II.

Considering the higher number of relapses in patients treated with the less-intensive P-III, at least a subpopulation in the SR
group was fairly undertreated with P-III. This refers particularly to
the inferior outcome of patients ≥10 years of age and those with
ETV6-RUNXI negative precursor B-cell ALL, which suggests
a greater effect in subsets with known unfavorable characteristics
despite the very favorable early response depicted by highly sen-
sitive PCR-MRD.

In patients in the prognostically more favorable subgroups, such as those with ETV6-RUNXI–positive ALL and those 1 to 6
years of age at diagnosis, the hazard ratios for the incidence of
relapse did not indicate an increase in the relapse rate, with the
disadvantage of treatment reduction possibly being negligible (Fig
4B). The same can be seen in patients treated with dexamethasone
during induction.

### Table 2. Clinically Relevant Adverse Events Related to Delayed Intensification Therapy

<table>
<thead>
<tr>
<th>Event</th>
<th>No. (%)</th>
<th>4-Year Cumulative Incidence, % (SE)</th>
<th>8-Year Cumulative Incidence, % (SE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>P-II (n = 584)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death in first CR</td>
<td>5 (0.9)</td>
<td>0.9 (0.4)</td>
<td>0.9 (0.4)</td>
</tr>
<tr>
<td>All relapses</td>
<td>50 (8.6)</td>
<td>6.3 (1.0)</td>
<td>8.7 (1.2)</td>
</tr>
<tr>
<td>Isolated BM</td>
<td>26 (4.5)</td>
<td>2.8 (0.7)</td>
<td>4.8 (0.9)</td>
</tr>
<tr>
<td>Isolated CNS</td>
<td>7 (1.2)</td>
<td>0.9 (0.4)</td>
<td>1.0 (0.4)</td>
</tr>
<tr>
<td>Isolated testes</td>
<td>5 (0.9)</td>
<td>0.9 (0.4)</td>
<td>0.9 (0.4)</td>
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<tr>
<td>Combined BM/CNS</td>
<td>6 (1.0)</td>
<td>0.7 (0.3)</td>
<td>0.9 (0.4)</td>
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<tr>
<td>Combined BM/other†‡</td>
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<td>1.0 (0.4)</td>
<td>1.0 (0.4)</td>
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<tr>
<td>Other relapses‡</td>
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<td>0.0 (0.0)</td>
<td>0.0 (0.0)</td>
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<tr>
<td>Secondary neoplasms</td>
<td>7 (1.2)</td>
<td>1.0 (0.4)</td>
<td>1.3 (0.5)</td>
</tr>
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</table>

Abbreviations: BM, bone marrow; CR, complete response; HR, hazard ratio; P-II, protocol II; P-III, protocol III.

*Fisher’s exact test was used for deaths and Gray’s test for relapses and secondary neoplasms.
†Other relapse sites comprise testis, eye, lymph node, and bone.
‡Other relapses comprise abdominal and orary.

### DISCUSSION

The attempt to reduce chemotherapy burden by choosing P-III as
a lower-intensity delayed intensification in patients considered to
be at low relapse risk did not succeed because outcome results were
inferior to those obtained with the standard treatment. DFS data
showed a significantly higher proportion of events in the experi-
mental arm, especially for patients who were ETV6-RUNXI negative or ≥10 years of age. In addition, the expected benefit of
reduced-intensity treatment in terms of acute toxicity and rates of
second malignancy could not be demonstrated. In fact, toxicity
seems to be virtually the same in both treatment arms. A possible
explanation for this observation is a less stringent handling of
patients in P-III by the treating physicians, which is probably
attributable to an underestimation of the impact of this treatment
(n = 173 with data available), respectively; 15 and 36 days were the
expected time according to protocol, respectively.
The current randomization was designed on the basis of the results of the ALL-BFM 81 and ALL-BFM 83 trials, which were the first by our study group that introduced a reintensification regimen called protocol 3 in the SR groups. Furthermore, these two trials documented the distinct importance of delayed intensification for the prevention of relapse.\textsuperscript{1,18,27} Hence, in subsequent trials, reintensification became an integral element of ALL treatment by using the more intensive version of reintensification (P-II) from ALL-BFM 86.\textsuperscript{1,28} In the current trial (AIEOP-BFM ALL 2000), P-III was randomized against the latter to find an approximation toward a less-intensive, but still-effective treatment.

Most recently, the Dutch Childhood Oncology Group (DCOG) reported the results of its study DCOG ALL10 with nonrandomized treatment reduction for SR patients during delayed intensification.\textsuperscript{31} The risk stratification criteria in this trial were similar to those in our trial. Treatment of SR patients was also comparable except for the reduced delayed intensification phase, which was considerably more reduced in intensity in that trial than in P-III. With reduced-intensity chemotherapy at a median follow-up of 80 months, 194 patients had a 5-year pEFS rate of 93.1 ± 1.9\% and 5-year CIR rate of 6.4 ± 1.85\%. The outcome results in this rather small cohort were interpreted as improvement compared with historical controls of the DCOG, and therapy reduction was declared as safe by study criteria. However, the pEFS was inferior, although not significant, to the results of the historical MRD-SR group as reported by the International BFM Study Group\textsuperscript{3} (5-year pEFS, 98\%; SE, 2\%; n = 55; \(P = .08\)).

Of note, the rates of 5-year pEFS and 5-year CIR in the DCOG study were in between the respective results of P-III (5-year pDFS, 90.6 ± 1.2\% [\(\Delta = 2.5\%\)]; 5-year CIR, 7.5 ± 1.1\% [\(\Delta = 1.1\%\)]\) and P-II (5-year pDFS, 94.9 ± 0.9\% [\(\Delta = 1.8\%\)]; 5-year CIR, 4.1 ± 0.8\% [\(\Delta = -2.3\%\)]) of the AIEOP-BFM ALL 2000 trial. This finding leaves open the question of whether the reduced intensity in the DCOG study is really noninferior to standard treatment with P-II.

In the study Malaysia-Singapore ALL 2003\textsuperscript{s}, risk stratification was likewise based on PCR-MRD by basically using the same risk stratification criteria as in our and the DCOG ALL10 protocols. SR patients were treated with a nonrandomized reduced therapy on the backbone of the ALL-Intercontinental BFM 2002 protocol.\textsuperscript{13,29} The treatment included a three-drug induction without anthracyclines as well as a reduced reinduction roughly comparable to P-III as reported here. With a rather short median follow-up of 3.38 years, the SR group of 172 patients had a 6-year pEFS rate of 93.2 ± 4.1\% and a 6-year OS rate of 95.4 ± 3.3\%, which depicts major improvement with the reduced-intensity treatment approach compared with preceding results of this study group along with a lower incidence of fatal and/or life-threatening treatment-related events. With the lack of a randomized approach, however, these improvements hardly could be differentiated from general improvements in quality of treatment and supportive care.

A randomized approach was chosen in the protocol of the British study group trial UKALL 2003, where 521 low-risk patients assessed by NCI criteria and PCR-MRD were randomly assigned to receive either one or two delayed intensification courses.\textsuperscript{12} With a median follow-up of 57 months, a difference in 5-year pEFS rate of 1.1\% was reported (94.4\% ± 95.5\%). The 95\% CI of the difference was −5.6\% to 2.5\%. The authors concluded that the primary end point of the randomization (to rule out a 7\% reduction in EFS) was achieved. With the noninferiority margin of 4\% in the current trial, this would not be true. Defining a reasonable noninferiority margin is always a matter of debate.

Another randomized treatment question about delayed intensification was asked by the US Children's Oncology Group. Comparability with the aforementioned trials and our study, however, is even more limited because MRD was not used for risk stratification.\textsuperscript{10} The authors demonstrated that the addition of a second delayed intensification in the treatment schedule of NCI SR patients with rapid early cytogic marrow response did not offer an advantage in terms of 5-year pEFS and OS rate (90.9 ± 1.3\% and 97.1 ± 0.8\% vs 90.5 ± 1.3\% and 95.4 ± 3.8\% for single and double delayed intensification, respectively).

In summary, both of the latter-cited trails—UKALL 2003 and COG 1991—revealed the feasibility of treatment reduction in patients with the most favorable prognosis in a randomized approach. Discrepancies with the results presented here might be explained by a fairly different treatment approach. A higher treatment intensity in the reduced intensity arm with single delayed intensification, which is comparable with P-II in the current study, presumably is a critical threshold that has not been reached. Differences in the risk stratification approaches also hamper comparability with the current trial.\textsuperscript{11,13,28}

As a future perspective, a constant refining of biologic subtypes and treatment response is warranted to ensure the best possible treatment stratification throughout study groups. Insertion of novel drugs in chemotherapeutic regimens and implementation of targeted therapies, such as leukemia-specific antibodies, hopefully will take their place in the treatment of SR leukemia and thus enable a reduction of conventional drugs. In particular, by sparing anthracyclines and alkylating agents, the reduction of acute and long-term toxicity could be achieved. However, as the results of the presented trial demonstrate, future development should be implemented carefully by means of randomized trials designed to recruit sufficiently large cohorts to enable detection of clinically relevant differences.

**Authors' Disclosures of Potential Conflicts of Interest**

Disclosures provided by the authors are available with this article at jco.org.

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Reduced-Intensity Delayed Intensification in Standard-Risk Pediatric Acute Lymphoblastic Leukemia Defined by Undetectable Minimal Residual Disease: Results of an International Randomized Trial (AIEOP-BFM ALL 2000)

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